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Original Research

Investigation of the utility of dynamic contrast MRI in predicting pathological response to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer

Dynamic MRI in predicting pathological response in rectal cancer

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Abstract
Aim: The study aimed to evaluate the utility of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)-derived semi-quantitative perfusion parameters obtained before treatment in predicting pathological response to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer.
Material and Method: The study included 93 patients with locally advanced rectal cancer who underwent DCE-MRI before treatment and whose pathological response to treatment was recorded. Rectal MRIs were evaluated retrospectively and simultaneously by two radiologists based on consensus. The mesorectal fascia (MRF) invasion and extramural vascular invasion (EMVI) of the tumors were assessed. Tumor length was measured in the sagittal or coronal plane using the T2-weighted sequence, considering the longest diameter of the tumor. The correlation of semi-quantitative parameters obtained from DCE-MRI and other MRI findings with pathological response to neoadjuvant chemoradiotherapy was also investigated.
Results: EMVI findings were observed in 28 (30.1%) patients, and MRF involvement in 15 (16.1%). The rates of T3 and T4 in T staging and those of N2 in N staging were found to be higher in groups with no response to neoadjuvant therapy compared to responders. Among the dynamic MRI parameters evaluated, the best diagnostic test performance for responders belonged to wash-out, followed by wash-in. The AUC values were calculated respectively at %96.4 [%95 CI (0.903-0.992)] and % 94.3 [%95 CI (0.903-0.992)].
Discussion: Wash-in and wash-out rates, semi-quantitative parameters of dynamic MRI taken before neoadjuvant chemoradiotherapy, can be used to predict pathological response to treatment.

Keywords
Rectal Cancer, Dynamic MRI, Pathological Response, Neoadjuvant Chemoradiotherapy

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Introduction

In rectal cancer, appropriate staging is important for both treatment planning and prognosis [1]. Magnetic resonance imaging (MRI) is the most commonly used modality for local staging of rectal cancer and determining appropriate treatment. Studies have shown that dynamic contrast-enhanced MRI (DCE-MRI) is effective in evaluating the presence of malignant neovascularity with varying diffusion and perfusion properties [2, 3]. The early identification of pathological outcomes using non-invasive, quantitative, and semi-quantitative measures is crucial for cost savings in the development of new target drugs [4]. Neoadjuvant chemoradiotherapy (CRT) has become standard in locally advanced stages of rectal cancer (T3c-d, T4, or N involvement) and mesorectal fascia (MRF) invasion [5]. Predicting the response to treatment in patients given neoadjuvant CRT is important in treatment planning and disease prognosis [6]. Although MRI is used as the standard method in the primary staging of rectal cancer in many centers, its role in examining treatment response is not yet clearly understood. With the widespread use of MRI in cancer patients, regression in tumor size and stage has been achieved, as well as a decrease in recurrence and an increase in life expectancy [7, 8]. European criteria are applied in the definition of locally advanced rectal cancer. The perfusion parameters of DCE-MRI have an important place in this process since the hemodynamics of the contrast medium may reflect both vascular fraction and permeability [5, 9].

This study aimed to evaluate the utility of semi-quantitative perfusion parameters derived from DCE-MRI taken before treatment in predicting pathological response to neoadjuvant CRT in patients with locally advanced rectal cancer.

Material and Methods

Patient Selection and Study Design

This retrospective study was carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. The requirement for informed consent from the patients was waived due to the retrospective nature of the study.

In this study, patients who were pathologically diagnosed with rectal cancer at the oncology or surgical oncology departments between January 2018 and November 2022 were screened, and 291 patients were identified.

Capecitabine (2×825 mg/m^2) was administered to the patients, as the chemotherapeutic agent. The dose required for radiotherapy in rectal cancer to treat microscopic disease with conventional fractionation is 45–50.4 Gy. These standard neoadjuvant chemoradiotherapy protocols recommended in the literature were applied to all patients [7,8]. All patients underwent surgery 12 weeks after the end of neoadjuvant therapy. All of the patients included in the study were patients with locally advanced rectum ca, and cases with distant metastases were not included in the study. The modified Ryan scoring system was utilized for pathological evaluation (8). When pathological response scores of 0 and 1 were combined, these patients were considered responders in a single group [2-4].

Imaging Technique

The following imaging protocol was used to create images: matrix, 268x259; field of view (FOV), 350 mm; slice thickness, 5 mm, slice distance, 0.8 mm; and repetition time (TR)/echo time (TE), 4,608/100 ms for the T2-weighted axial sequence; matrix, 220x205; FOV, 220 mm; slice thickness, 3 mm; slice distance, 0.5 mm; and TR/TE, 3,299/110 ms for the T2-weighted sagittal sequence; matrix, 312x186; FOV, 250 mm; slice thickness, 4 mm; slice distance, 0.4 mm; and TR/TE, 5,760/100 ms for the T2-weighted coronal sequence; matrix, 312x224; FOV, 250 mm; slice thickness, 4 mm; slice distance, 0.4 mm; and TR/TE, 514/8 ms for the pre- and post-contrast x T1-weighted axial and sagittal sequences; and matrix, 220x223; FOV, 240 mm; TR/TE, 6.0/1.88; dynamic scanning time, 00:10.5 s; and k0 time 00:03.0 s for the dynamic T1-weighted axial sequence.

In all patients, 0.1 mmol/kg of gadoteric acid (Dotarem®) was intravenously administered at a rate of 2 ml/sec via an antecubital vein with an automatic injector. After the intravenous contrast agent injection, 15 ml of physiological saline was administered at the same rate. Semi-quantitative parameters were obtained by calculating the contrast agent concentration. The evaluation was performed by retrospectively screening the images from the picture archiving and communication systems of the hospital. For imaging, a 1.5T MRI device (Philips Ingenia, Best, Eindhoven, Netherlands, 2017) and a phased array superficial body coil were used.

MRI Evaluation

In our center, considering the time required for the tumor to regress, in accordance with the clinical guidelines of the European Society for Medical Oncology, the best time for total mesorectal excision (TME) is considered to be six to eight weeks after the end of CRT; therefore, TME surgery was performed according to this schedule. The patients' rectal MRIs taken before neoadjuvant therapy were evaluated. The evaluation was carried out simultaneously and retrospectively by two radiologists, one with four and the other with 20 years of experience in radiology. Tumor localization was divided into three groups: low (0-5 cm from the anal verge), middle (5-10 cm from the anal verge), and high (10-15 cm from the anal verge). The staging of the patients was undertaken based on the T and N evaluation criteria using the MRI images. Lymph nodes larger than 5 mm in diameter were evaluated pathologically in terms of lymph node involvement. Thoracoabdominal computed tomographic (CT) examinations were performed to evaluate distant organ metastases. MRF invasion and extramural vascular invasion (EMVI) of the tumor were evaluated using conventional images. Tumor volume was measured in sections where the tumor was best visualized on T2-weigted sequences. Volumetric evaluation was performed using regions of interest (ROI) and measuring the tumor area separately for each section. Tumor length was measured in the sagittal or coronal plane in the T2-weighted sequence, considering the longest diameter of the tumor. The images were evaluated on a workstation (Intelli Space Philips, the Netherlands).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) v. 25.0 software package was used for the statistical analyses of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where appropriate). The Shapiro-Wilk test was used to determine

whether the parameters in the study showed a normal distribution. The chi-square and Fisher's exact tests were used to compare categorical variables. The one-way analysis of variance test was conducted for the analysis of the differences between the groups in the presence of normally distributed variables, and the Kruskal-Wallis test was used in those that did not show a normal distribution. The post hoc Bonferroni test was employed to examine the source of the difference between the groups. Lastly, a receiver operating characteristic (ROC) curve analysis was applied to determine the power of the investigated parameters to predict pathological response. The statistical significance level was taken as 0.05 in all tests.

Ethical Approval

This study was approved by the Ethics Committee of University of Health Sciences Turkey, Adana City Training and Research Hospital and the Turkish Ministry of Health (Date: 2021-12-30, No: 1709).

Results

After excluding patients who were not suitable for evaluation, 93 patients with locally advanced rectal cancer who underwent DCE-MRI before treatment and whose pathological response to treatment was recorded were included in the study (Figure 1).

The mean age of the patients was 62.0 ± 11.3 years, and 59 (63.4%) were male. Tumor localization was found to be low in 25 (26.9%) patients, middle in 44 (47.3%), and high in 24 (25.8%). EMVI findings were observed in 28 (30.1%) of the patients, and MRF involvement in 15 (16.1%). The mean tumor length was 5.13 ± 1.4 cm, and the mean tumor volume was 30.2 ± 8.7 cm3. Of all patients, 64 (68.8%) were included in

Table 1. Demographic and MRI data of the patients

	n	%
Gender		
Female	34	36.6
Male	59	63.4
Tumor localization		
Low	25	26.9
Middle	44	47.3
High	24	25.8
T stage		
T2	26	28.0
T3	56	60.2
T4	11	11.8
N stage		
N0	40	43.0
N1	44	47.3
N2	9	9.7
EMVI		
Absent	65	69.9
Present	28	30.1
MRF involvement		
Absent	78	83.9
Present	15	16.1
	Mean ± Sd	**Med (Min-Max)**
Age	62.0 ± 11.3	65 (31-78)
Tumor length (cm)	5.13 ± 1.4	5 (1.5-9)
Tumor volume (cm3)	30.2 ± 8.7	29.7 (12.6-55.6)

EMVI: Extramural vascular invasion, MRF: Mesorectal fascia, Sd: Standard deviation, Med: Median, Min: Minimum, Max: Maximum

Table 2. Comparison of the investigated parameters between the pathological response groups

	Responders (n = 29)	Minimal response (n = 34)	No response (n = 30)	p
Tumor localization, n (%)				
Low	8 (27,6)	12 (35,3)	5 (16,7)	0,269,†
Middle	13 (44,8)	17 (50)	14 (46,7)	
High	8 (27,6)	5 (14,7)	11 (36,7)	
T stage, n (%)				
T2	19 (65,5)	5 (14,7)	2 (6,7)	<0,001**,†
T3	10 (34,5)	26 (76,5)	20 (66,7)	
T4	-	3 (8,8)	8 (26,7)	
N stage, n (%)				
N0	8 (27,6)	18 (52,9)	14 (46,7)	0,014*,†
N1	21 (72,4)	12 (35,3)	11 (36,7)	
N2	-	4 (11,8)	5 (16,7)	
EMVI, n (%)				
Absent	27 (93,1)	22 (64,7)	16 (53,3)	0,003**,†
Present	2 (6,9)	12 (35,3)	14 (46,7)	
MRF involvement, n (%)				
Absent	29 (100)	28 (82,4)	21 (70)	0,007**,†
Present	-	6 (17,6)	9 (30)	
Tumor length (cm) (mean ± Sd)	4,13±1,2a,b	5,27±1,1a	5,94±1,4b	<0,001**,‡
Tumor volume (cm^3) (mean ± Sd)	23,0±5,9a,b	31,7±6,8a	35,5±8,4b	<0,001**,‡

EMVI: Extramural vascular invasion, MRF: Mesorectal fascia, Sd: Standard deviation
*p < 0.05, **p < 0.001, †Chi-square and Fisher's exact tests, ‡Kruskal-Wallis test; post hoc Bonferroni test

Table 3. Evaluation of the diagnostic test performance of the investigated parameters using the receiver operating characteristic curve analysis

	T stage	N stage	EMVI	MRF involvement
AUC (95%CI)	0.803 (0.707-0.878)	0.561 (0.454-0.664)	0.669 (0.563-0.763)	0.617 (0.511-0.716)
Sensitivity (95% CI)	89.06 (78.8-95.5)	50 (37.2-62.8)	40.63 (28.5-53.6)	23.44 (13.8-35.7)
Specificity (95% CI)	65.52 (45.7-82.1)	72.41 (52.8-87.3)	93.10 (77.2-99.2)	100.0 (88.1-100)
PPV (95% CI)	85.1 (77.4-90.5)	80 (67.9-88.3)	92.9 (76.8-98.1)	100 (100-100)
NPV (95% CI)	73.1 (56.2-85.1)	39.6 (32-47.8)	41.5 (36.2-47.1)	37.2 (34.1-40.4)
P	<0.001**	0.261	<0.001**	<0.001**

EMVI: Extramural vascular invasion, MRF: Mesorectal fascia, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval
*p < 0.05, **p < 0.001

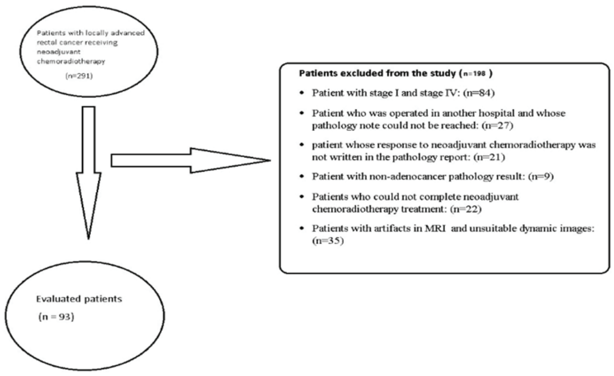

Figure 1. The initial overall number of patients, together with the number of patients included in the study, is demonstrated. The number of patients excluded from the study and exclusion criteria of the study are shown

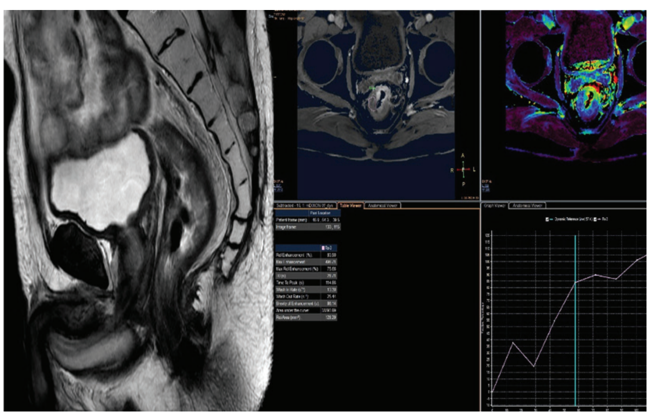

Figure 2. Sagittal T2 images and dynamic magnetic resonance imaging parameters of a 57-year-old female patient with a 4.3-cm, T2N1 tumor located in the lower rectum with no response to neoadjuvant chemoradiotherapy; T0 (s): 28.71, TTP: 114.86 s-1, wash-in rate: 13.30 s-1, and wash-out rate; 25.44 s-1

the non-responder group, and 29 (31.2%) in the responder group. Minimal response was detected in 34 (36.6%) of the 64 patients evaluated in the non-responder group (Table 1). There was no significant difference between the tumor localization of the responder and non-responder groups (p = 0.269). In T staging, the rates of T3 and T4 were higher in the non-response and minimal response groups compared to the responders (p < 0.001). In N staging, the rate of N2 was higher in patients with no response and minimal response compared to responders (p = 0.014). The rates of EMVI and MRF involvement were found to be higher in the groups with no response and minimal response than in responders (p = 0.003 and p = 0.007, respectively) (Table

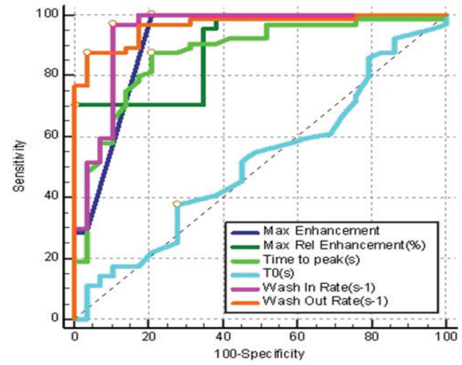

Figure 3. Receiver operating characteristic curves of dynamic MRI parameters for pathological response

2). There was a significant difference between the groups in terms of tumor length and tumor volume (p < 0.001 for both). When the source of significance was examined with the post hoc Bonferroni test, it was determined that tumor length and tumor volume were lower in responders than in patients with no response and those with minimal response (p < 0.05) (Table 2). Table 3 presents the diagnostic test performances of T stage, N stage, EMVI, and MRF involvement for pathological response. In this analysis, at their respective cut-off points, the AUC values of T stage, N stage, EMVI, and MRF involvement were calculated to be 80.3, 56.1, 66., and 61.7, respectively. Accordingly, the best diagnostic test performance belonged to the T stage. The following perfusion parameters were evaluated: (1) maximum enhancement, (2) maximum relative enhancement; (3) T0 (s), (4) time to peak (s), (5) wash-in rate (s-1), and (6) wash-out rate (s-1) (Figure 2). In the examination of the diagnostic test performances of maximum enhancement, Maximum enhancement ratio (%), time to peak (s), T0 (s), wash-in rate (s-1), and wash-out rate (s-1) for pathological response, the AUC values of these parameters were determined to be 91.5%, 89.2%, 87.3%, 51.4%, 94.3%, and 96.4%, respectively, at their respective cut-off points. Accordingly, the best diagnostic test performance belonged to wash-out rate, followed by wash-in rate (Figure 3).

Discussion

It has been reported that the degree of angiogenesis in a tumor is associated with tumor grading and aggressiveness, which are associated with prognosis and treatment response [12-14]. According to the results of the study, among dynamic MRI parameters, maximum enhancement, maximum enhancement ratio, time to peak, and wash-in and wash-out rates were lower in patients with complete response than in those with

no response or minimal response to CRT. In addition, the ROC curve analysis revealed the best diagnostic test performance for the wash-out rate at 96.4%, followed by the wash-in rate at 94.3%. Since highly differentiated tumors have denser vascular structures, they permit a greater exchange between the blood bed and the interstitial space due to the more efficient passage and permeability of various substances, including MRI contrast [14-16]. Therefore, as tumor aggressiveness increases, parameters measured in dynamic MRI are lower than in non-aggressive tumors [17, 18]. In a study including 51 cases, Ciolina et al. [14] found these parameters to be low in those with pathological complete response. In addition, the authors noted the best diagnostic test performance in the wash-out value at 95%. In another study evaluating 90 patients, Phongkitkarun et al. [5] reported that the maximum enhancement and time to peak values were lower in the group with pathological response to neoadjuvant therapy with a sensitivity of 95%. In a study of 95 cases, Oberholzer et al. [16] found that the time to peak value obtained from dynamic contrast MRI was successful in predicting pathological response with 95% sensitivity. Consistent with the literature, our results demonstrated that the wash-out and wash-in rates were the most successful parameters in predicting response to neoadjuvant therapy.

In a study including 34 cases, Gollub et al. [8] reported that T and N stages were lower in the group with pathological response. In another study of 71 cases, Sengul et al. [18] determined that tumors with low T and N stages showed a higher rate of pathological response compared to those with high T and N stages. Similarly, Johnston et al. [19] found that a low T stage was associated with pathological response at a sensitivity of 78.9% in 44 patients. Our results support the literature data in that when T and N staging was performed according to conventional MRI findings before CRT, the rates of T3, T4, and N2 were found to be higher in patients with no response and those with minimal response ($p = 0.014$).

In a study conducted by Tong et al. [20] with 38 patients, it was determined that as tumor length increased, pathological response to neoadjuvant CRT decreased. In a comprehensive study covering 405 cases, Yeo et al. [21] reported that as tumor volume increased, pathological response to neoadjuvant CRT decreased, and the cut-off value of tumor volume was 23.1 cm^3 with 95% sensitivity. Similarly, Palmisano et al. [22] observed that pathological response decreased as tumor volume increased, and the cut-off value of tumor volume was 21.55 cm^3 with 92% sensitivity. Our results are in agreement with those reported in the literature. The ROC curve test revealed the cut-off values of tumor length and tumor volume to be >4.4 cm and >23.8 cm^3, respectively. Accordingly, the sensitivity of tumor volume was found to be 95.31% in predicting pathological response.

In a study found EMVI positivity before CRT to be higher among patient groups with no pathological response at a sensitivity of 95% in a total of 100 cases [23]. The authors also noted that the rate of patients with MRF involvement was higher among non-responders. This has been proven to be an indicator of poor prognosis in patients with rectal cancer presenting with EVMI and MRF involvement, as well as showing the biological aggressiveness of cancer [22]. In the current study, the rates of EMVI and MRF involvement were higher in patients with no response and those with minimal response compared to the responders, which is consistent with the literature.

Limitation

There are some limitations to our study. First, although measurements were performed by two radiologists using ROI, individual differences that might occur due to manual measurements cannot be overlooked. Second, in the current literature, k_{trans}, v_e, and k_{ep} calculations have been used to describe DCE-MRI parameters, where ktrans correlates with the initial slope (wash-in rate) of the time intensity curve, ve correlates with the peak height and time to peak of the time intensity curve, and kep controls the shape of the curve (reflected in the relative contributions of its independent components, K_{trans} and v_e); however, we were not able to use these quantitative parameters since there is no software in our hospital that could calculate these values. This can be considered a limitation in terms of the inability to compare related data with the existing literature. Lastly, due to the single-center and retrospective design of the study, the generalizability of our findings is limited.

Conclusion

Wash-in and wash-out rates, which are semi-quantitative parameters of dynamic MRI taken before neoadjuvant CRT, are successful in predicting pathological response to treatment. Patients with locally advanced stage rectal cancer who have high T and N stages, as well as those with EMVI and MRF involvement, tend to have a lower pathological response to neoadjuvant CRT.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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